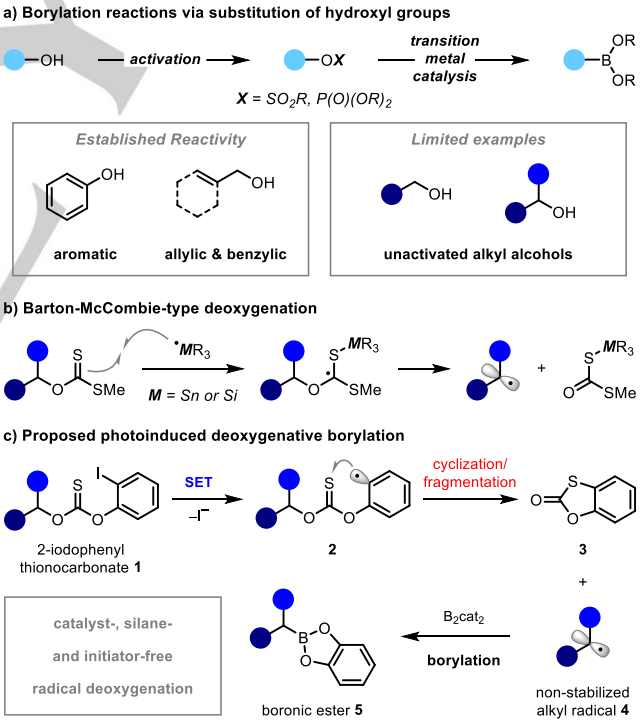
Photoinduced Deoxygenative Borylations of Aliphatic Alcohols

Jingjing Wu, Robin M. Bär, Lin Guo, Adam Noble, and Varinder K. Aggarwal*[a]

Abstract: A photochemical method for converting aliphatic alcohols into boronic esters is described. Preactivation of the alcohol as a 2-iodophenyl-thionocarbonate enables a novel Barton-McCombie-type radical deoxygenation that proceeds efficiently with visible light irradiation and without the requirement for a photocatalyst, a radical initiator, or tin or silicon hydrides. The resultant alkyl radical is intercepted by bis(catecholato)diboron, furnishing boronic esters from a diverse range of structurally complex alcohols.

Alkylborons are some of the most useful reagents in synthetic chemistry because of the versatile reactivity of carbon–boron bonds.[1] As a result, bench-stable derivatives, such as boronic esters and potassium trifluoroborate salts, are used extensively across organic synthesis,[2] materials science,[3] and medicinal chemistry.[4] These are typically prepared from prefunctionalized substrates via substitution of halides[5] or borylation reactions of alkenes.[6] The introduction of boronic ester groups into complex molecules by substitution of abundant native functional groups represents a highly attractive alternative strategy. Recent progress in this area has provided new methods to access alkylboronic esters from carboxylic acids and primary amines.[7,8] These reactions proceed via single electron transfer (SET)-induced fragmentation of activated substrates (*N*-hydroxyphthalimide esters or *N*-alkylpyridiniums) to generate alkyl radicals, which are subsequently borylated. Conversely, radical-mediated borylations of alcohols have been developed to a much lesser extent, despite the abundance of this motif and the established methods available for deoxygenative alkyl radical formation.[9,10]

The most common approach to convert alcohols into boronic esters is the transition metal-catalyzed Miyaura borylation, which requires initial conversion of the alcohol to a pseudohalide (Scheme 1a).[11] However, this approach is limited to aryl[12] and activated (allyl or benzyl) alkyl alcohol derivatives.[13,14] Recently, Fu and co-workers reported a silver-catalyzed radical borylation of primary and secondary unactivated alkyl tosylates, which requires elevated temperatures and activation of the diboron reagent with strong base.[9a] We considered an alternative transition metal-free borylation strategy that could proceed under mild conditions by taking advantage of radical deoxygenations of xanthates or *O*-alkyl thionocarbonates.[10a] Such Barton-McCombie-type deoxygenations are promoted by attack of a tin or silicon radical at the sulfur atom of the thiocarbonyl moiety (Scheme 1b). However, we postulated that the use of tin or silicon reagents could be avoided by using 2-iodophenyl-thionocarbonates **1**, wherein the radical deoxygenation could be initiated by SET-induced cleavage of the carbon–iodine bond (Scheme 1c). The resulting high energy aryl radical **2** could undergo 5-*endo*-trig cyclization and fragmentation to provide cyclic thionocarbonate **3** and alkyl radical **4**, which would be intercepted with bis(catecholato)diboron (B_2cat_2) to yield boronic ester **5**. During the course of our studies, Studer and co-workers disclosed a Barton-McCombie-inspired deoxygenative radical borylation of activated alcohols with B_2cat_2, which either required stoichiometric AIBN and $(Me_3Si)_3SiH$ or the use of an iridium photoredox catalyst.[15] Herein, we report that using iodinated substrate **1** allows catalyst-free deoxygenative borylations to proceed simply with visible light irradiation, without the need for a stoichiometric radical initiator or silane.



Scheme 1. Deoxygenative borylation reactions.

We initiated our deoxygenative borylation studies by investigating the reaction of 4-hydroxypiperidine-derived thionocarbonate **1a** with B_2cat_2 (Table 1). Using the operationally simple and mild photochemical conditions that have proved successful in decarboxylative,[7a] deaminative,[8a] and deiodinative[5f,16] borylations, we were delighted to observe productive deoxygenative borylation, with pinacol boronic ester

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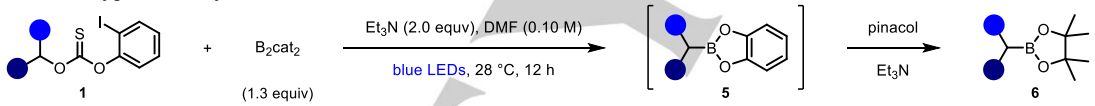
6a obtained in 19% yield after transesterification of the initially formed catechol boronic ester with pinacol (entry 1). Hydrodeoxygenation product **7** was also observed in trace amounts, presumably via hydrogen atom transfer (HAT) between the alkyl radical intermediate and solvent. Given the established application of photoredox catalysts in dehalogenation reactions of aryl halides,[17] we examined their effectiveness in promoting the borylation reaction. We were pleased to find that using catalytic $Ir(ppy)_3$ improved the yield of **6a** to 56% (entry 2, see Supporting Information for a survey of other photocatalysts). Adding Et_3N to the reaction increased the yield further to 67% (entry 3), in line with previous reports of trialkyl amines facilitating dehalogenations under photoredox catalysis.[17] Interestingly, using Et_3N in the absence of photocatalyst still provided **6a** in 50% yield (entry 5). Intrigued by this result, and the attractive prospect of performing this deoxygenation borylation reaction under photocatalyst-free conditions, we investigated alternative light sources and found that the integrated photoreactor developed by Merck and the MacMillan group yielded **6a** in a much improved 80% yield (entry 5).[18] Furthermore, the reaction time could be reduced to just 3 h using this more efficient photochemical setup (entry 6). Finally, control experiments highlighted the importance of Et_3N (see Supporting Information for a survey of other bases) and a reaction in the dark showed that an inefficient thermal reaction was also operative (entries 7–8).

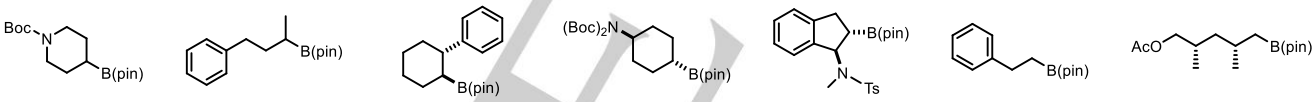
Table 1. Optimization studies.[a]

entry	additive	light source	% **6a**	% **7**
1	-	24 W strips	19	1
2	1 mol% $Ir(ppy)_3$	24 W strips	56	5
3	1 mol% $Ir(ppy)_3$, 2.0 equiv Et_3N	24 W strips	67	3
4	2.0 equiv Et_3N	24 W strips	50	<1
5[b]	2.0 equiv Et_3N	photoreactor	80	1
6[c]	2.0 equiv Et_3N	photoreactor	76	1
7[b]	-	photoreactor	34	12
8[d]	2.0 equiv Et_3N	none	15	0

[a] All reactions were performed with **1a** (0.10 mmol) and B_2cat_2 (1.3 equiv) in DMF (1.0 mL). Light sources were 24 W blue LED strips (reaction temperature = 40 °C) or the integrated photoreactor described in ref. 18 (reaction temperature = 28 °C). Yields were determined by GC analysis using an internal standard. [b] Irradiated for 12 h. [c] Irradiated for 3 h. [d] Reaction performed at 25 °C in the dark.

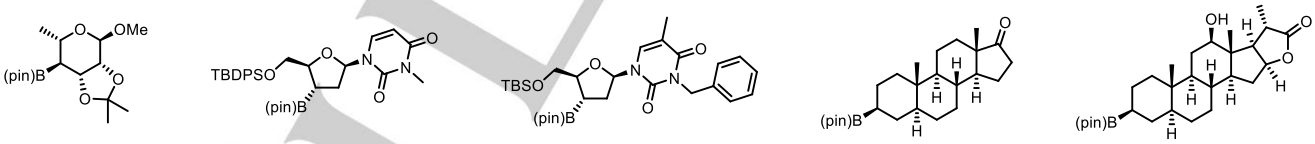
Table 2. Scope of the deoxygenative borylation reaction.[a]



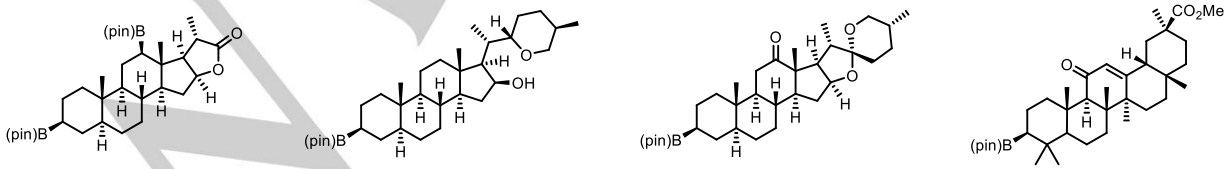


6a: 72% (65%)[b] **6b**: 85% **6c**: 66%, >95:5 d.r. **6d**: 61%, 87:13 d.r. **6e**: 65%, >95:5 d.r.[c] **6f**: 34%[d] **6g**: 32%[d]

6h: 32%[d] **6i**: 44%[c] **6j**: 79%, >95:5 d.r. *[from menthol]* **6k**: 35%, >95:5 d.r.[e] *[from borneol]* **6l**: 36%, 52:48 d.r. *[from 4-hydroxyproline]* **6m**: 60%, >95:5 d.r.[d] *[from Corey lactone]*



6n: 45%, >95:5 d.r. *[from rhamnose]* **6o**: 46%, >95:5 d.r. *[from 2'-deoxyuridine]* **6p**: 57%, >95:5 d.r. *[from thymidine]* **6q**: 61%, 93:7 d.r. *[from epiandrosterone]* **6r**: 73%, 95:5 d.r. *[from rockogenin]*



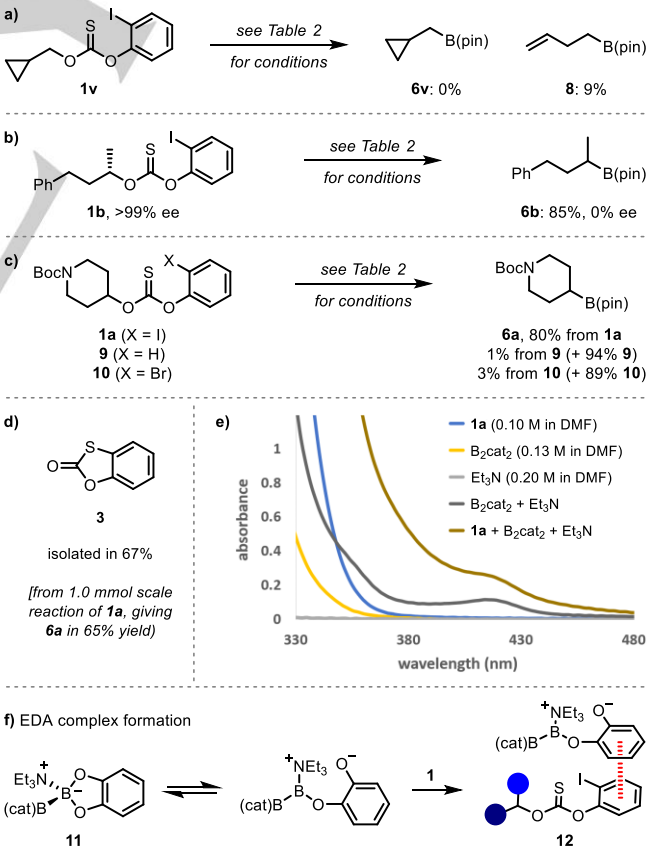
6s: 43%, >95:5 d.r.[c,f] *[from rockogenin]* **6t**: 62%, 91:9 d.r. *[from tigogenin]* **6u**: 61%, 92:8 d.r. *[from hecogenin]* **6v**: 64%, >95:5 d.r.[c] *[from glycyrrhetinic acid]*

[a] Reactions were carried out with 0.1–0.2 mmol of thionocarbonate **1**. See Supporting Information for exact conditions. Yields are of isolated products. Diastereomeric ratios were determined by ^1H NMR analysis of the oxidized products. [b] Number is parentheses shows yield of a 1.0 mmol scale reaction. [c] Using 2.6 equiv B_2cat_2. [d] Reaction carried out at 60 °C for 18–24 h. [e] Using 1.0 mol% $Ir(ppy)_3$. [f] Using 0.05 mmol of thionocarbonate **1s**.

With the optimized conditions in hand, we investigated the scope of the reaction using a range of thionocarbonates **1** (Table 2). Substrates derived from both cyclic and acyclic secondary alcohols furnished the boronic ester products (**6a**–**6e**) in good yield, with disubstituted cyclohexanes **6c** and **6d** and indane **6e** also formed in high diastereoselectivity. The reaction was also scalable, with product **6a** formed in 65% yield on a 1.0 mmol scale. Primary boronic esters **6f**–**6h** could also be prepared using this method, although the yields were low, likely reflecting the challenging formation of non-stabilized primary radicals. Adamantanol-derived tertiary boronic ester **6i** was formed in moderate yield, however, other tertiary alcohols could not be used since tertiary thionocarbonates readily undergo Chugaev elimination.[19] Given the prevalence of aliphatic alcohols in nature, we proceeded to prepare boronic esters from a range of structurally diverse natural products. The terpenes menthol and borneol were borylated to give **6j** and **6k** in moderate to high yield and with excellent diastereoselectivity. Hydroxyproline could be converted into amino acid derivative **6l** in moderate yield. Using Corey's prostaglandin precursor **1m** provided **6m** in good yield, with the borylation unexpectedly occurring with high selectivity for the concave face of the molecule, presumably due to the steric hindrance of the α-substituent. Carbohydrates were also suitable substrates, with highly diastereoselective deoxygenative borylations providing derivatives of rhamnose (**6n**), and the nucleosides deoxyuridine (**6o**) and thymidine (**6p**). The latter example is noteworthy as it generates a borylated analogue of azidothymidine (AZT), one of the original treatments of HIV/AIDS. The boronic acid derived from **6p** is likely to have interesting biological properties itself, but the C–B bond of **6p** can also be transformed stereospecifically into a host of alternative analogues. Finally, a range of steroid derivatives (**6q**–**6v**) were prepared in good yields and diastereoselectivity, including a double deoxygenative borylation to form bis-boronic ester **6s**. Interestingly, the silver-catalyzed borylation protocol recently described by Fu and co-workers provided boronic esters **6q** and **6u** in 74:26 and 58:42 d.r.,[9a] respectively, whereas we observed ≥92:8 d.r. using our catalyst-free conditions. It should be noted that for some sterically hindered boronic esters (e.g. **6e**, **6i** and **6v**, increased equivalents of B_2cat_2 were required due to competing HAT, which gave hydrodeoxygenation products **7**.[20]

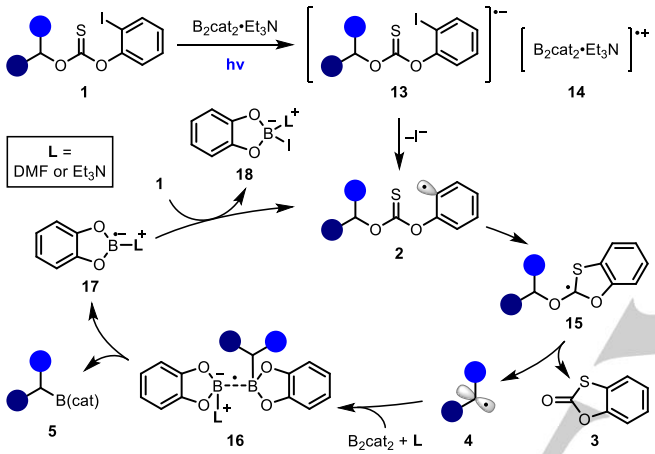
To probe the mechanism of the borylation reaction, we performed a radical clock experiment with cyclopropylmethyl thionocarbonate **1v**, which gave ring-opened boronic ester **8** as the only observed product, confirming the formation of alkyl radical intermediates (Scheme 2a). Further support was provided by enantioenriched substrate **1b** providing **6b** as a racemic mixture (Scheme 2b). The importance of the iodide on thionocarbonates **1** was confirmed by control experiments using non-halogenated and brominated analogues **9** and **10**, which failed to provide more than trace boronic ester **1a** under the standard conditions (Scheme 2c). These results rule out a mechanism proceeding via direct single electron reduction of the thiocarbonyl moiety and suggest that the more challenging reduction of aryl bromides compared to iodides inhibits photoinduced electron transfer of **10**. Evidence for the proposed 5-*endo*-trig cyclization/fragmentation of aryl radical intermediates (see **2** in Scheme 1c) was provided upon isolating cyclic thionocarbonate **3** (Scheme 2d).

We subsequently investigated the photoinitiation process by measuring absorption spectra of the reaction components. Thionocarbonate **1a** absorbs only weakly in the visible region (Scheme 2e) and displayed no significant interaction with B_2cat_2 or Et_3N.[20] Interestingly, while B_2cat_2 and Et_3N individually do not absorb light in the visible region, a large bathochromic shift occurred upon mixing the two, with a new peak observed at 416 nm (Scheme 2e). Addition of **1a** to this mixture caused an even more dramatic shift, significantly increasing the intensity of the peak at 416 nm and leading to substantial absorbance at 450 nm, the wavelength of the LEDs used in our reaction. This suggests the formation of a ternary complex, which could also be observed visually, as a DMF solution of **1a**, B_2cat_2 and Et_3N changed from colourless to pale yellow within 1 minute of mixing. We then performed a series of ^{11}B and ^{13}C NMR experiments that suggested the complex is formed via a Lewis acid–base adduct (**11**) between Et_3N and one of the boron atoms of B_2cat_2, which increases the electron density on one of the catecholate ligands to enable a π–π interaction with the aryl iodide of **1** and results in the formation of an electron donor–acceptor (EDA) complex (**12**, Scheme 2f).[20,21] Further evidence for the formation of adduct **11** and complex **12** was provided by cyclic voltammetry.[20]



Scheme 2. Mechanistic studies.

Based on these observations, we propose the mechanism shown in Scheme 3. Irradiation of EDA complex **12** formed between thionocarbonate **1**, B_2cat_2 and Et_3N results in photoinduced electron transfer to generate aryl iodide radical anion **13** and radical cation complex **14**. Elimination of iodide from **13** provides aryl radical **2**, which after 5-*endo*-trig cyclization and subsequent fragmentation of **15**, gives alkyl radical **4** and cyclic thionocarbonate **3**. Borylation of **4** likely proceeds via the same pathway as previously described[5f,8,16] with homolytic substitution at boron of B_2cat_2 (via **16** with a weak B–B one electron σ-bond) facilitated by either DMF or Et_3N. The resulting Lewis base stabilized boryl radical **17** can then react with thionocarbonate **1**, either via iodine atom abstraction[5f] or SET,[8c] to regenerate aryl radical **2** and form the I–Bcat Lewis base adduct **18**.



Scheme 3. Proposed mechanism.

In conclusion, we have developed a deoxygenative borylation reaction which proceeds efficiently under mild, operationally simple conditions, with only a slight excess of the diboron reagent. The process is noteworthy in that it does not require a photocatalyst, a radical initiator, or a silyl hydride. The methodology shows high functional group tolerance, enabling a broad array of alcohol-containing natural products to be converted into boronic esters, often with high stereocontrol.

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Keywords: Boronic Esters • Borylation • Deoxygenation • Photochemistry • Radical Reactions

[1] a) C. Sandford, V. K. Aggarwal, *Chem. Commun.* **2017**, *53*, 5481; b) *Boronic Acids: Preparation and Applications in Organic Synthesis Medicine and Materials, Vols. 1 and 2* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2011**.

[2] a) D. Leonori, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2015**, *54*, 1082; *Angew. Chem.* **2015**, *127*, 1096; b) G. A. Molander, *J. Org. Chem.* **2015**, *80*, 7837; c) J. W. B. Fyfe, A. J. B. Watson, *Chem* **2017**, *3*, 31.

[3] W. L. A. Brooks, B. S. Sumerlin, *Chem. Rev.* **2016**, *116*, 1375.

[4] a) P. C. Trippier, C. McGuigan, *MedChemComm* **2010**, *1*, 183; b) R. Smoum, A. Rubinstein, V. M. Dembitsky, M. Srebnik, *Chem. Rev.* **2012**, *112*, 4156; c) D. B. Diaz, A. K. Yudin, *Nat. Chem.* **2017**, *9*, 731.

[5] a) A. S. Dudnik, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 10693; b) H. Ito, K. Kubota, *Org. Lett.* **2012**, *14*, 890; c) A. Joshi-Pangu, X. Ma, M. Diane, S. Iqbal, R. J. Kribs, R. Huang, C.-Y. Wang, M. R. Biscoe, *J. Org. Chem.* **2012**, *77*, 6629; d) S. K. Bose, K. Fucke, L. Liu, P. G. Steel, T. B. Marder, *Angew. Chem. Int. Ed.* **2014**, *53*, 1799; *Angew. Chem.* **2014**, *126*, 1829; e) T. C. Atack, S. P. Cook, *J. Am. Chem. Soc.* **2016**, *138*, 6139; f) Y. Cheng, C. Mück-Lichtenfeld, A. Studer, *Angew. Chem. Int. Ed.* **2018**, *57*, 16832; *Angew. Chem.* **2018**, *130*, 17074; g) Q. Liu, J. Hong, B. Sun, G. Bai, F. Li, G. Liu, Y. Yang, F. Mo, *Org. Lett.* **2019**, DOI: 10.1021/acs.orglett.9b01951.

[6] a) A.-M. Carroll, T. O. O'Sullivan, P. J. Guiry, *Adv. Synth. Catal.* **2005**, *347*, 609; b) H. E. Burks, J. P. Morken, *Chem. Commun.* **2007**, 4717; c) B. S. L. Collins, C. M. Wilson, E. L. Myers, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2017**, *56*, 11700; *Angew. Chem.* **2017**, *129*, 11860.

[7] a) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers, V. K. Aggarwal, *Science* **2017**, *357*, 283; b) C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science* **2017**, *356*, eaam7355; c) D. Hu, L. Wang, P. Li, *Org. Lett.* **2017**, *19*, 2770; d) J. Wang, M. Shang, H. Lundberg, K. S. Feu, S. J. Hecker, T. Qin, D. G. Blackmond, P. S. Baran, *ACS Catal.* **2018**, *8*, 9537.

[8] a) J. Wu, L. He, A. Noble, V. K. Aggarwal, *J. Am. Chem. Soc.* **2018**, *140*, 10700; b) J. Hu, G. Wang, S. Li, Z. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 15227; *Angew. Chem.* **2018**, *130*, 15447; c) F. Sandfort, F. Strieth-Kalthoff, F. J. R. Klauck, M. J. James, F. Glorius, *Chem. Eur. J.* **2018**, *24*, 17210.

[9] a) X. Lu, Z.-Q. Zhang, L. Yu, B. Zhang, B. Wang, T.-J. Gong, C.-L. Tian, B. Xiao, Y. Fu, *Chin. J. Chem.* **2019**, *37*, 11; b) Mazzarella, G. Magagnano, B. Schweitzer-Chaput, P. Melchiorre, *ACS Catal.* **2019**, *9*, 5876.

[10] a) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574; b) D. Crich, L. Quintero, *Chem. Rev.* **1989**, *89*, 1413; c) W. Hartwig, *Tetrahedron*, **1983**, *39*, 2609.

[11] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508.

[12] a) T. Ishiyama, Y. Itoh, T. Kitano, N. Miyaura, *Tetrahedron Lett.* **1997**, *38*, 3447; b) M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *J. Org. Chem.* **2000**, *65*, 164; c) D. A. Wilson, C. J. Wilson, C. Moldoveanu, A.-M. Resmerita, P. Corcoran, L. M. Hoang, B. M. Rosen, V. Percec, *J. Am. Chem. Soc.* **2010**, *132*, 1800; d) G. A. Molander, L. N. Cavalcanti, C. García-García, *J. Org. Chem.* **2013**, *78*, 6427. For transition metal-free borylations of phenol derivatives promoted by UV light, see: c) W. Liu, X. Yang, Y. Gao, C.-J. Li, *J. Am. Chem. Soc.* **2017**, *139*, 8621; d) K. Chen, M. S. Cheung, Z. Lin, P. Li, *Org. Chem. Front.* **2016**, *3*, 875;

[13] a) T. Ishiyama, T. Ahiko, N. Miyaura, *Tetrahedron Lett.* **1996**, *37*, 6889; G. Dutheuil, N. Selander, K. J. Szabó, V. K. Aggarwal, *Synthesis* **2008**, 2293; b) Z.-C. Cao, F.-X. Luo, W.-J. Shi, Z.-J. Shi, *Org. Chem. Front.* **2015**, *2*, 1505; c) T. C. Atack, R. M. Lecker, S. P. Cook, *J. Am. Chem. Soc.* **2014**, *136*, 9521.

[14] For a copper-catalyzed borylation of unactivated alkyl tosylates via initial in situ conversion to the corresponding alkyl iodide, see: C.-T. Yang, Z.-Q. Zhang, H. Tajuddin, C.-C. Wu, J. Liang, J.-H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder, L. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 528; *Angew. Chem.* **2012**, *124*, 543.

[15] F. W. Friese, A. Studer, *Angew. Chem. Int. Ed.* **2019**, *58*, 9561; *Angew. Chem.* **2019**, *131*, 9661.

[16] Y. Cheng, C. Mück-Lichtenfeld, A. Studer, *J. Am. Chem. Soc.* **2018**, *140*, 6221.

[17] For selected examples, see: a) J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanam, C. R. J. Stephenson, *Nat. Chem.* **2012**, *4*, 854; b) H. Kim, C. Lee, *Angew. Chem. Int. Ed.* **2012**, *51*, 12303; *Angew. Chem.* **2012**, *124*, 12469; c) J. J. Devery, III, J. D. Nguyen, C. Dai, C. R. J. Stephenson, *ACS Catal.* **2016**, *6*, 5962.

[18] C. Le, M. K. Wismer, Z.-C. Shi, R. Zhang, D. V. Conway, G. Li, P. Vachal, I. W. Davies, D. W. C. MacMillan, *ACS Cent. Sci.* **2017**, *3*, 647.

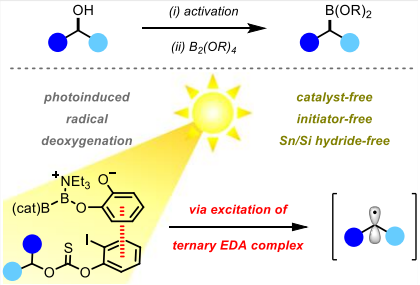
[19] M. J. Fuchter in *Name Reactions for Functional Group Transformations* (Ed.: J. J. Li), Wiley: New York, **2007**, pp. 334−342.

[20] See Supporting Information for details.

[21] a) B. Liu, C.-H. Lim, G. M. Miyake, *J. Am. Chem. Soc.* **2017**, *139*, 13616; b) K. Liang, N. Li, Y. Zhang, T. Li, C. Xia, *Chem. Sci.* **2019**, *10*, 3049; c) C. G. S. Lima, T. de M. Lima, M. Duarte, I. D. Jurberg, M. W. Paixão, *ACS Catal.* **2016**, *6*, 1389.

COMMUNICATION

Visible light irradiation of 2-iodophenyl-thionocarbonates enabled Barton-McCombie-type radical deoxygenations to proceed in the absence of a photocatalyst, a radical initiator, or tin or silicon hydrides. Applying this strategy to deoxygenative borylation reactions allowed a wide range of structurally diverse aliphatic alcohols to be transformed into synthetically valuable boronic esters.



*Jingjing Wu, Robin M. Bär, Lin Guo, Adam Noble, Varinder K. Aggarwal**

Page No. – Page No.

Photoinduced Deoxygenative Borylations of Aliphatic Alcohols